VIA EFS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent Application of: Ann Margaret DYER et al.	§		
	§	Group Art Unit:	1616
Conf. No.: 1191	§		
	§		
Appln. No.: 10/598,212	§	Examiner:	David Browe
	§		
Filing Date: August 21, 2006	§	Attorney Docket No.:	10774-88US
	§		(ARCCX/P32619US)
	§		

Title: CHITOSAN CONTAINING SOLUTION

DECLARATION OF PETER JAMES WATTS, Ph.D. UNDER 37 C.F.R. § 1.132

I, Peter James Watts, declare as follows:

1. My present position is Director, Pharmaceutical Development, working for Archimedes Development Limited ("Archimedes"), an English company, and the assignee of the present application, where the invention of the above-identified application was invented, and though I am not an inventor of this invention, I am very aware of its conception and development and it is now a part of my portfolio of responsibilities for Archimedes. I have worked in the research and development of pharmaceutical formulations from 1992 to the present day.

2. I hold degrees of Bachelor of Science in Pharmacy from Aston University, United Kingdom and Doctor of Philosophy in Pharmaceutics from Nottingham University, United Kingdom. I consider myself an expert with respect to intranasal drug delivery compositions, including chitosan-containing compositions, and believe that others would also consider me to be such an expert. I have been named as an author on several papers relating to nasal drug administration, including the use of chitosan in compositions for intranasal drug delivery.

3. I have read and understand the above-identified application and the prior art documents to which the Examiner has referred. I have read and understand the Amendment being submitted with this Declaration.

4. The present invention is directed to a composition for delivery of systemically-acting therapeutic agents to a mucosal surface, where such compositions comprise chitosan or the claimed derivatives, salts and salts of derivatives of chitosan, along with a polyol-phosphate or sugar-phosphate salt and a plasticizer, for effective delivery of the therapeutic agent nasally or ocularly. One of the unique features of the compositions of the invention is that they are in the form of an aqueous solution or suspension prior to use, but form a gel at physiological temperatures, such that a gel is formed shortly after application to the mucosal surface of the nose or eye. Thus, a way to assess the suitability of certain compositions for delivery of the systemically-acting therapeutic agent is to determine which plasticizer results in a gel in physiological temperature conditions, for humans a temperature of about 35°C to about 37°C at the mucosal surface of the nasal cavity or eye, to which the therapeutic agent is delivered. By forming a gel at the mucosal surface, the therapeutic agent passes more effectively into the systemic circulation of the animal to which the systemically-acting therapeutic agent is administered or delivered since the period of time which the composition remains in contact with the mucosal surface is increased. This is a surprising and unexpected feature of the combination of the chitosan polyol-phosphate or sugar-phosphate salt and the triethyl citrate.

5. During the research work that lead to the development of the present invention, a series of tests was conducted within Archimedes using a variety of plasticizers to determine which plasticizers were suitable for use in the present invention. A summary of the work conducted by Archimedes accompanies this Declaration as Annex A.

6. As noted in Annex A, ten plasticizers were tested under substantially identical conditions. Briefly, a first solution was prepared containing chitosan glutamate and the plasticizer being tested. A second solution was prepared containing β-glycerophosphate. The first solution was chilled in an ice bath and the second solution added and mixed vigorously with the first solution, followed by mixing in water. A sample of each final mixture was then dropped onto each of two glass microscope slides. One slide was incubated at 35°C and the other at 37°C and the samples were observed for evidence of gel formation over a 15 minute period.

7. As noted in the Table of Annex A, several of the compounds tested as plasticizers were not soluble in the aqueous solutions, so they were not suitable for use in the composition. Several others did not result in a solution that gelled at either temperature. The PEG materials prohibited gel formation at high concentrations and provided slow, incomplete gel formation at lower concentrations.

8. Although compositions containing triacetin gelled at 35°C and 37°C, gel formation was slow compared to the composition containing triethyl citrate as the plasticizer. Rapid gelling at the temperature found in the eye or in the nose is advantageous for ocular and nasal drug delivery compositions, as this reduces loss of the composition caused by the composition dripping out of the eye or nose; the drug remains in contact with the mucosa for a longer period, thus increasing the effectiveness of absorption.

9. Based on the research and results summarized above and shown in Annex A, the inventors, unpredictably and therefore very surprisingly, found unique properties when triethyl citrate is used as a plasticizer in a composition comprising chitosan, a salt thereof or a derivative thereof as defined in claim 1 and a polyol-phosphate or sugar-phosphate salt in an aqueous solution or suspension that can be administered or delivered to an animal, including humans, in the form of a spray or drops as also set forth in claim 1. The data of Annex A show that the effect of using various plasticizers, and particularly triethyl citrate, is not at all predictable. When triethyl citrate is used as a plasticizer in the composition, the viscosity of the composition increases rapidly at physiological temperatures to form a gel, which should enable a systemically-acting therapeutic agent to be more effectively delivered to the systemic circulation, whereas other known plasticizers did not result in a composition that had such a rapid increase in viscosity to quickly form a gel.

10. The prior art references cited by the Examiner, whether considered alone or together, do not disclose or even suggest the use of triethyl citrate to alter and enhance the gelling properties of a composition comprising a chitosan, salt, derivative or salt of the derivative and polyol phosphate or sugar-phosphate salt which is delivered in the form of spray or drops. A conclusion of obviousness, therefore, cannot be based on cited references and would be entirely speculative, when viewing the references as a whole

against the claimed invention as a whole. No one could have reasonably predicted the success at rapid gelling of the composition in the form of an aqueous solution under physiological temperature conditions provided by the triethyl citrate. The present invention was not obvious to the inventors and others at Archimedes working on the project of this invention, and would not have been obvious to others of ordinary or even extraordinary skill in the art of pharmaceutical delivery systems.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present application or any patent issued thereon.

Signed: P. J. Watts This 12th day of November 2010

Peter James Watts

ANNEX A

Evaluation of Alternative Plasticizer Compounds

The following procedure was performed:

- A first solution was prepared containing 21.7 mg/ml chitosan glutamate and the plasticizer. Unless otherwise indicated, the concentration of plasticizer in this solution was 5.75 mg/ml.
- A second solution was prepared containing 150 mg/ml β-glycerophosphate.
- 4.6 ml of the chitosan / plasticiser solution was chilled in an ice bath and 0.5 ml of β-glycerophosphate solution added slowly with vigorous stirring followed by 0.21 ml of water: The final mixture contained 18.9 mg/ml chitosan glutamate, 5 mg/ml of plasticizer and 14.2 mg/ml of β-glycerophosphate.
- A 0.1 ml sample of the mixture was then dropped onto each of two glass microscope slides. One slide was placed into an incubator at 35°C and the other at 37°C. The samples were observed for evidence of gel formation over a 15 minute period, with the results set forth in the following Table:

<table>
<tr><th>Plasticizer Compound</th><th>Experimental observation</th></tr>
<tr><td>Tributyl citrate</td><td>Unsuitable: Not soluble in water.</td></tr>
<tr><td>Acetyl tributyl citrate</td><td>Unsuitable: Not soluble in water.</td></tr>
<tr><td>Acetyl triethyl citrate</td><td>Unsuitable: Not soluble in water.</td></tr>
<tr><td>Dibutyl sebacate</td><td>No gel was formed when chitosan / β-glycerophosphate solution was warmed to 35°C and 37°C.</td></tr>
<tr><td>Glycerol</td><td>No gel was formed when chitosan / β-glycerophosphate solution was warmed to 35°C and 37°C.</td></tr>
<tr><td>Propylene glycol</td><td>No gel was formed when chitosan / β-glycerophosphate solution was warmed to 35°C and 37°C.</td></tr>
<tr><td>PEG 400 and PEG 8000*</td><td>High concentrations inhibited gel formation. Slow and incomplete gel formation at lower concentrations.</td></tr>
<tr><td>Triacetin</td><td>Gel was formed when chitosan / β-glycerophosphate solution was warmed to 35°C and 37°C. However, gel formation was slow compared to formulation containing triethyl citrate as plasticizer:
<table>
<tr><th rowspan="2">Plasticizer</th><th colspan="2">Gel formation time</th></tr>
<tr><th>35°C</th><th>37°C</th></tr>
<tr><td>Triacetin</td><td>5-10 minutes</td><td>10-15 minutes</td></tr>
<tr><td>Triethyl citrate</td><td>Less than 5 minutes</td><td>Less than 5 minutes</td></tr>
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*Concentrations of PEG 400 and 8000in the final formulation were in the range 5-15 mg/ml.